

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
8 July 2004 (08.07.2004)

PCT

(10) International Publication Number
WO 2004/056365 A3

(51) International Patent Classification⁷: A61K 31/498, C07D 403/06, 239/82, 403/10, 409/06, 405/06, 417/06, 401/06, 413/06, 401/12, 239/78, C07C 49/84, A61P 5/18

Sven [DE/DE]; Adlergässchen 6, 79539 Lörrach (DE). WIDLER, Leo [CH/CH]; Melchior-Berri Strasse 11, CH-4142 Muenchenstein (CH).

(21) International Application Number:
PCT/EP2003/014741

(74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(22) International Filing Date:
22 December 2003 (22.12.2003)

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(25) Filing Language: English
(26) Publication Language: English

(30) Priority Data:
0230015.0 23 December 2002 (23.12.2002) GB

(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

(71) Applicant (for all designated States except AT, US): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
(71) Applicant (for AT only): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

Published:

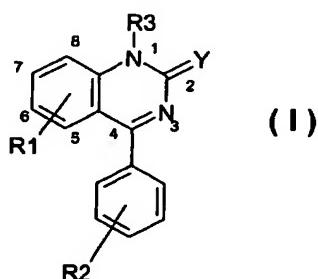
- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventors; and
(75) Inventors/Applicants (for US only): ALTMANN, Eva [CH/CH]; Tannenweg 5, CH-4153 Reinach (CH). BEERLI, René [CH/CH]; Kirchweg 29, CH-4102 Binningen (CH). GERSPACHER, Marc [CH/CH]; Grossmatt 8, CH-4616 Kappel (CH). RENAUD, Johanne [CA/CH]; Nussbaumweg 24, CH-4103 Bottmingen (CH). WEILER,

(88) Date of publication of the international search report:
19 August 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DERIVATIVES OF ARYL-QUINAZOLINE/ARYL-2AMINO-PHENYL METHANONE WHICH PROMOTE THE RELEASE OF PARATHYROID HORMONE



(I)

(57) Abstract: A compound of formula (I): wherein R1, R2, R3 and Y are as defined herein, or a pharmaceutically-acceptable and -cleavable ester, or acid addition salt thereof, useful for promoting the release of parathyroid hormone, e.g. for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

WO 2004/056365 A3

23 JUN 2005

INTERNATIONAL SEARCH REPORT

10/540359

International Application No

PCT/EP 03/14741

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/498	C07D403/06	C07D239/82	C07D403/10	C07D409/06
C07D405/06	C07D417/06	C07D401/06	C07D413/06	C07D401/12
C07D239/78	C07C49/84	A61P5/18		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RUSSELL, R. K. ET AL: "Synthesis and renal vasodilator activity of substituted '4-alkyl(aryl)-2-oxoquinazolin-1-yl!alkanoic acids" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 3, 1992, pages 277-284, XP002935850 page 284, left-hand column; examples 30, 31	1,2
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280288 retrieved from STN accession no. 1306 Database accession no. 1980:121782 rn:73052-29-6 abstract	3-8
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280288 retrieved from STN accession no. 1306 Database accession no. 1980:121782 rn:73052-29-6 abstract	1,2
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

8 June 2004

Date of mailing of the International search report

18/06/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gavriliu, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& MIYAGISHI, AKIRA ET ALL: "General pharmaceutical studies on ciproquazone (SL-573) and its metabolites" OYO YAKURI, vol. 18, no. 1, 1979, pages 9-22,	
X	MASAI, NARUHITO ET AL: "Carbon-13 nuclear magnetic resonance studies of anti-inflammatory 2(1H)-quinazolinones" CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 25, no. 11, 1977, pages 3018-3022, XP009000437 examples 3,4,6-10,12	1,2
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280289 retrieved from STN accession no. 1406 Database accession no. 1982:503745 rn:37554-38-4 abstract & S. MARDENTE, C. BICCHI, M.G.NANO: "GLC-ECD determination of 1-(2-hydroxyethyl)-3-hydroxy-7-chloro-1,3-dihydro-5-(0-fluorophenyl)-2H-1,4-benzodiazepin-2-one (SAS 643) in plasma and urine and identification of its main biotransformation products" THERAPEUTIC DRUG MONITORING, vol. 3, no. 4, 1981, pages 351-356,	1,2
X	US 4 387 223 A (YAMAMOTO MICHIIRO ET AL) 7 June 1983 (1983-06-07) column 4, lines 5,36	1,2
A	column 2, lines 12-17	5-8
X	CH 612 186 A (SUMITOMO CHEMICAL CO) 13 July 1979 (1979-07-13) page 4, left-hand column, lines 1,7,32; claim 1	1,2
X	US 3 812 257 A (INAHA S ET AL) 21 May 1974 (1974-05-21) column 9, lines 10-70	1,2
A	column 3, line 67 column 4, lines 1,3,6,52	3-8
X	GB 1 353 789 A (SUMITOMO CHEMICAL CO) 22 May 1974 (1974-05-22) page 2, left-hand column, lines 25-39 page 4, right-hand column, lines 68,7174 page 5, lines 47,76,82	1,2
A		3-8
		-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280290 retrieved from STN accession no. 1142 Database accession no. 1994:244939 rn:154374-68-2P; 154374-67-1 abstract & M.I. JAEDA AT ALL: "Synthesis of some novel 2(1H)-quinazolinones and 2-thioxo analog from newly synthesized 1-acyl-3-alkoxyphenylureas and tioureas" JOURNAL OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY, vol. 58, no. 4, 1993, pages 391-394,</p> <p>-----</p>	1,2
X	US 5 773 663 A (REHNIG ANNEROSE EDITH ELISE ET AL) 30 June 1998 (1998-06-30)	3,4
A	column 36, line 60 - column 40, line 65; example 115 column 1, line 35 - column 2, line 30	1,2,5-8
X	US 5 856 503 A (MAERKI HANS-PETER ET AL) 5 January 1999 (1999-01-05)	3,4
A	column 16, line 53 - column 20, line 45; example 35	1,2,4-8
X	<p>DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002280291 retrieved from STN accession no. 1277 Database accession no. 1981:461773 rn:78350-38-6 abstract & JP 55 143959 A (SHIONOGI AND CO.) 10 November 1980 (1980-11-10)</p> <p>-----</p>	3,4
X	<p>DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002280292 Database accession no. 6810088 abstract & B.BERGER, M.BOLTE: ACTA CRYSTALLOGR. SECT.C: CRYST. STRUCT. COMMUN, vol. 50, 1994, pages 773-775,</p> <p>-----</p>	3,4
A	US 3 925 548 A (HANS OH, PFEFFINGEN) 9 December 1975 (1975-12-09) column 10, line 52 - column 12, line 15; claims; examples 9,15	1-8
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/14741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/24683 A (JANSSEN PHARMACEUTICA NV ;ANGIBAUD PATRICK RENE (FR); VENET MARC G) 28 March 2002 (2002-03-28) page 72-compounds 'B6!', 'B20! page 77, lines 2-12; claims -----	1-8
A	US 6 211 244 B1 (DELMAR ERIC G ET AL) 3 April 2001 (2001-04-03) claims; figures -----	1-8
P,X	WO 02/102782 A (NOVARTIS AG, SWITZ.;NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H) 27 December 2002 (2002-12-27) the whole document -----	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/14741

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: -

Present Claims 1 and 3 relate to an extremely large number of possible compounds. In fact, Claims 1 and 3 contain so many options, variables, possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT arises to such an extent as to render a meaningful search of the above-mentioned claims impossible. The claims 1 and 3 can in no way be considered to be a reasonable generalisation of the actual examples since it include numerous possibilities which cannot be considered as equivalents, homologues or analogues of the examples. Consequently, the search was carried out for those parts of the application which do appear to be clear (concise and supported by the examples), namely for the compounds for which R1 is a 2-propynyloxy, methoxy or hydroxy moiety and R3 is an optionally substituted alkyl, alkenyl or benzyl. All the examples have been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/14741

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 4387223	A	07-06-1983	JP AT AT AU CA CH DE DK FR GB HU MX NL SE SE	52071483 A 352737 B 915976 A 2016476 A 1068694 A1 602667 A5 2656156 A1 553076 A ,B, 2376142 A1 1510270 A 173530 B 3930 E 7613307 A 422578 B 7613839 A	14-06-1977 10-10-1979 15-03-1979 10-11-1977 24-12-1979 31-07-1978 23-06-1977 12-06-1977 28-07-1978 10-05-1978 28-06-1979 01-10-1981 14-06-1977 15-03-1982 12-06-1977
CH 612186	A	13-07-1979	JP JP AT AT CA CH DK HU NL SE SE	51008287 A 54016506 B 342600 B 525775 A 1046063 A1 612186 A5 318075 A ,B, 170223 B 7507921 A 414404 B 7507922 A	23-01-1976 22-06-1979 10-04-1978 15-08-1977 09-01-1979 13-07-1979 14-01-1976 28-04-1977 15-01-1976 28-07-1980 14-01-1976
US 3812257	A	21-05-1974	NONE		
GB 1353789	A	22-05-1974	JP AT AU AU BE CA CH DD DE FR HU NL SE SU US	51018423 B 319919 B 448048 B2 3634071 A 776332 A1 1002046 A1 558800 A 95841 A5 2159655 A1 2117301 A5 163952 B 7116769 A 397518 B 517242 A3 4096144 A	09-06-1976 10-01-1975 09-05-1974 07-06-1973 04-04-1972 21-12-1976 14-02-1975 20-02-1973 22-06-1972 21-07-1972 28-11-1973 12-06-1972 07-11-1977 05-06-1976 20-06-1978
US 5773663	A	30-06-1998	US US	5922919 A 5866722 A	13-07-1999 02-02-1999
US 5856503	A	05-01-1999	BR CA CN EP JP TR	9605906 A 2190708 A1 1161328 A ,B 0778271 A2 9176123 A 970475 A2	18-08-1998 09-06-1997 08-10-1997 11-06-1997 08-07-1997 21-06-1997
JP 55143959	A	10-11-1980	NONE		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/14741

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 3925548	A	09-12-1975	US	B313531 I5	28-01-1975
			AT	319949 B	10-01-1975
			AT	319950 B	10-01-1975
			AT	310176 B	25-09-1973
			AT	310169 B	25-09-1973
			BE	741529 A	11-05-1970
			CH	520145 A	15-03-1972
			CH	520686 A	31-03-1972
			CH	520687 A	31-03-1972
			CH	520688 A	31-03-1972
			CH	520690 A	31-03-1972
			CH	520691 A	31-03-1972
			CH	521972 A	30-04-1972
			DE	1956384 A1	11-06-1970
			DK	130738 B	07-04-1975
			DK	130739 B	07-04-1975
			DK	129347 B	30-09-1974
			ES	373377 A1	16-05-1972
			ES	387024 A1	01-12-1973
			ES	387025 A1	01-12-1973
			ES	387026 A1	01-12-1973
			ES	387027 A1	01-12-1973
			ES	387028 A1	01-12-1973
			ES	387029 A1	16-11-1973
			ES	387030 A1	16-11-1973
			ES	387031 A1	16-11-1973
			ES	387032 A1	16-11-1973
			ES	387033 A1	01-06-1974
			ES	387034 A1	01-06-1974
			FR	2024830 A5	04-09-1970
			GB	1282612 A	19-07-1972
			IE	33933 B1	11-12-1974
			IL	33348 A	30-04-1973
			NL	6916514 A	14-05-1970
			NO	124032 B	21-02-1972
			OA	3829 A	24-12-1971
			PH	9553 A	16-01-1976
			PL	72695 B1	30-08-1974
			SE	376917 B	16-06-1975
			SE	374920 B	24-03-1975
			SU	366612 A3	16-01-1973
			SU	376942 A3	05-04-1973
			SU	365889 A3	08-01-1973
			US	3723432 A	27-03-1973
			ZA	6907910 A	28-07-1971
WO 0224683	A	28-03-2002	AU	9382901 A	02-04-2002
			WO	0224683 A1	28-03-2002
			EP	1322636 A1	02-07-2003
			JP	2004509884 T	02-04-2004
			US	2004048882 A1	11-03-2004
US 6211244	B1	03-04-2001	US	6011068 A	04-01-2000
			AT	264292 T	15-04-2004
			AU	709303 B2	26-08-1999
			AU	4195796 A	15-05-1996
			AU	702629 B2	25-02-1999
			AU	8087294 A	08-05-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/14741

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 6211244	B1		BR 9509411 A	30-12-1997
			CA 2202879 A1	02-05-1996
			CN 1220658 A	23-06-1999
			CZ 9701182 A3	17-09-1997
			CZ 292709 B6	12-11-2003
			DE 69433714 D1	19-05-2004
			EP 1203761 A2	08-05-2002
			EP 1275635 A1	15-01-2003
			EP 0724561 A1	07-08-1996
			EP 0787122 A2	06-08-1997
			JP 11130737 A	18-05-1999
			JP 9504032 T	22-04-1997
			JP 2882882 B2	12-04-1999
			JP 10513436 T	22-12-1998
			NZ 297157 A	30-08-1999
			PL 319812 A1	01-09-1997
			WO 9612697 A2	02-05-1996
			US 6001884 A	14-12-1999
			US 6313146 B1	06-11-2001
			US 6031003 A	29-02-2000
			US 5688938 A	18-11-1997
			US 5962314 A	05-10-1999
			HU 77980 A2	01-02-1999
			RU 2195446 C2	27-12-2002
			US 5858684 A	12-01-1999
			US 5763569 A	09-06-1998
WO 2002102782	A	27-12-2002	CA 2449234 A1	27-12-2002
			WO 02102782 A2	27-12-2002
			EP 1401451 A2	31-03-2004
			NZ 529716 A	19-12-2003